CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 40131

Trade Name Edrophonium Chloride Injection USP 10mg/ml 15ml Multiple Dose Vial

Generic Name Edrophonium Chloride Injection USP 10mg/ml 15ml Multiple Dose Vial

Sponsor Abbott Laboratories

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 40131

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)	X			
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)	X			
Correspondence		X		

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 40131

APPROVAL LETTER

ANDA 40-131

FEB 24 1998

Abbott Laboratories
Attention: Thomas F. Willer, Ph.D.
D-389 AP 30
200 Abbott Park Road
Abbott Park, IL 60064

Dear Sir:

This is in reference to your abbreviated new drug application dated December 30, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Edrophonium Chloride Injection USP, 10 mg/mL (15 mL Multiple Dose Vial).

Reference is also made to your amendments dated September 5, October 2 and December 19, 1997; and February 6, and 13, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Edrophonium Chloride Injection USP, 10 mg/mL to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Tensilon Injectable Solution, 10 mg/mL, of Hoffmann La Roche, Inc.).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

2-24-98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40131

FINAL PRINTED LABELING

PRECAUTIONS

Patients may develop "anticholinesterase insensitivity" for brief or prolonged periods. During these periods the patients should be carefully monitored and may need respiratory assistance. Dosages of anticholinesterase drugs should be reduced or withheld until patients again become sensitive to them.

ADVERSE REACTIONS

Careful observation should be made for severe cholinergic reactions in the hyperreactive individual. The myasthenic patient in crisis who is being tested with edrophonium chloride should be observed for bradycardia or cardiac standstill and cholinergic reactions if an overdose is given.

The following reactions common to anticholinesterase agents may occur, although not all of these reactions have been reported with the administration of edrophonium chloride, probably because of its short duration of action and limited indications:

Eye: Increased lacrimation, pupillary constriction, spasm of accommodation, diplopia, conjunctival hyperemia.

CNS: Convulsions, dysarthria, dysphonia, dysphagia.

Respiratory: Increased tracheobronchial secretions, laryngospasm, bronchiolar constriction, paralysis of muscles of respiration, central respiratory paralysis.

Cardiac: Arrhythmias (especially bradycardia), fall in cardiac output leading to hypotension.

G.I.: Increased salivary, gastric and intestinal secretion, nausea, vomiting, increased peristalsis, diarrhea, abdominal cramps.

Skeletal Muscle: Weakness, fasciculations.

Miscellaneous: Increased urinary frequency and incontinence, diaphoresis.

OVERDOSAGE

With drugs of this type, muscarine-like symptoms (nausea, vomiting, diarrhea, sweating, increased bronchial and salivary secretions and bradycardia) often appear with overdosage (cholinergic crisis). An important complication that can arise is obstruction of the airway by bronchial secretions. These may be managed with suction (especially if tracheostomy has been performed) and by the use of atropine. Many experts have advocated a wide range of dosages of atropine (for edrophonium chloride injection, see atropine dosage below), but if there are copious secretions, up to 1.2 mg intravenously may be given initially and repeated every 20 minutes until secretions are controlled. Signs of atropine overdosage such as dry mouth, flush and tachycardia should be avoided as tenacious secretions and bronchial plugs may form. A total dose of atropine of 5 to 10 mg or even more may be required. The following steps should be taken in the management of overdosage of edrophonium chloride injection:

1. Adequate respiratory exchange should be maintained by assuring an open airway and by the use of assisted respiration augmented by oxygen.
2. Cardiac function should be monitored until complete stabilization has been achieved.
3. Atropine sulfate in doses of 0.4 to 0.5 mg should be administered intravenously. This may be repeated every 3 to 10 minutes. Because of the short duration of action of edrophonium chloride injection the total dose required will seldom exceed 2 mg.
4. Pralidoxime chloride (a cholinesterase reactivator) may be given intravenously at the rate of 50 to 100 mg per minute; usually the total dose does not exceed 1000 mg. Extreme caution should be exercised in the use of pralidoxime chloride when the cholinergic symptoms are induced by double-bond phosphorous anticholinesterase drugs.[9]
5. If convulsions occur or shock is present, appropriate measures should be instituted.

DOSAGE AND ADMINISTRATION

Edrophonium Chloride Test in the Differential Diagnosis of Myasthenia Gravis:[1-6]

Intravenous Dosage (Adults): A tuberculin syringe containing 1 mL (10 mg) of edrophonium chloride is prepared with an intravenous needle, and 0.2 mL (2 mg) is injected intravenously within 15 to 30 seconds. The needle is left *in situ. Only* if no reaction occurs after 45 seconds is the remaining 0.8 mL (8 mg) injected. If a cholinergic reaction (muscarinic side effects, skeletal muscle fasciculations and increased muscle weakness) occurs after injection of 0.2 mL (2 mg), the test is discontinued and atropine sulfate, 0.4 mg to 0.5 mg, is administered intravenously. After one-half hour the test may be repeated.

Intramuscular Dosage (Adults): In adults with inaccessible veins, dosage for intramuscular injection is 1 mL (10 mg) of edrophonium chloride. Subjects who demonstrate hyperreactivity to this injection (cholinergic reaction), should be retested after one-half hour with 0.2 mL (2 mg) of edrophonium chloride intramuscularly to rule out false-negative reactions.

Dosage (Children): The intravenous testing dose of edrophonium chloride in children weighing up to 75 lbs is 0.1 mL (1 mg); above this weight, the dose is 0.2 mL (2 mg). If there is no response after 45 seconds, it may be titrated up to 0.5 mL (5 mg) in children under 75 lbs, given in increments of 0.1 mL (1 mg) every 30 to 45 seconds and up to 1 mL (10 mg) in heavier children. In infants, the recommended dose is 0.05 mL (0.5 mg). Because of technical difficulty with intravenous injection in children, the intramuscular route may be used. In children weighing up to 75 lbs, 0.2 mL (2 mg) is injected intramuscularly. In children weighing more than 75 lbs, 0.5 mL (5 mg) is injected intramuscularly. All signs which would appear with the intravenous test appear with the intramuscular test except that there is a delay of two to ten minutes before a reaction is noted.

Edrophonium Chloride Test for Evaluation of Treatment Requirements in Myasthenia Gravis: The recommended dose is 0.1 mL to 0.2 mL (1 mg to 2 mg) of edrophonium chloride, administered intravenously one hour after oral intake of the drug being used in treatment.[1-5] Response will be myasthenic in the undertreated patient, adequate in the controlled patient, and cholinergic in the overtreated patient. Responses to edrophonium chloride in myasthenic and nonmyasthenic individuals are summarized in the following chart:[2]

	Myasthenic*	Adequate†	Cholinergic‡
Muscle Strength (ptosis, diplopia dysphonia, dysphagia, dysarthria, respiration, limb strength)	Increased	No change	Decreased
Fasciculations (orbicularis oculi, facial muscles, limb muscles)	Absent	Present or absent	Present or absent
Side reactions (lacrimation diaphoresis, salivation, abdominal cramps, nausea, vomiting, diarrhea)	Absent	Minimal	Severe

***Myasthenic Response**– occurs in untreated myasthenics and may serve to establish diagnosis; in patients under treatment, indicates that therapy is inadequate.

†**Adequate Response**– observed in treated patients when therapy is stabilized; a typical response in normal individuals. In addition to this response in nonmyasthenics, the phenomenon of forced lid closure is often observed in psychoneurotics.[1]

‡**Cholinergic Response**– seen in myasthenics who have been overtreated with anticholinesterase drugs.

Edrophonium Chloride Injection Test in Crisis: The term *crisis* is applied to the myasthenic whenever severe respiratory distress with objective ventilatory inadequacy occurs and the response to medication is not predictable. This state may be secondary to a sudden increase in severity of myasthenia gravis (myasthenic crisis), or to overtreatment with anticholinesterase drugs (cholinergic crisis).

When a patient is apneic, controlled ventilation must be secured immediately in order to avoid cardiac arrest and irreversible central nervous system damage. No attempt is made to test with edrophonium chloride injection until respiratory exchange is adequate. *Dosage used at this time is most important:* If the patient is cholinergic, edrophonium chloride injection will cause increased oropharyngeal secretions and further weakness in the muscles of respiration. If the crisis is myasthenic, the test clearly improves respiration and the patient can be treated with longer-acting intravenous anticholinesterase medication. When the test is performed, there should not be more than 0.2 mL (2 mg) edrophonium chloride in the syringe. An intravenous dose of 0.1 mL (1 mg) is given initially. The patient's heart action is carefully observed. If, after an interval of one minute, this dose does not further impair the patient, the remaining 0.1 mL (1 mg) can be injected. If no clear improvement of respiration occurs after 0.2 mL (2 mg) dose, it is usually wisest to discontinue all anticholinesterase drug therapy and secure controlled ventilation by tracheostomy with assisted respiration.[5]

For Use as a Curare Antagonist: Edrophonium chloride should be administered by intravenous injection in 1 mL (10 mg) doses given slowly over a period of 30 to 45 seconds so that the onset of cholinergic reaction can be detected. This dosage may be repeated whenever necessary. The maximal dose for any one patient should be 4 mL (40 mg). Because of its brief effect, edrophonium chloride should not be given prior to the administration of curare, tubocurarine, gallamine triethiodide or dimethyl-tubocurarine; it should be used at the time when its effect is needed. When given to counteract curare overdosage, the effect of each dose on the respiration should be carefully observed before it is repeated, and assisted ventilation should always be employed.

DRUG INTERACTIONS

Care should be given when administering this drug to patients with symptoms of myasthenic weakness who are also on anticholinesterase drugs. Since symptoms of anticholinesterase overdose (cholinergic crisis) may mimic underdosage (myasthenic weakness), their condition may be worsened by the use of this drug. (See OVERDOSAGE section for treatment.)

HOW SUPPLIED

Edrophonium Chloride Injection, USP is available as:

15 mL Multiple-Dose Vials, 10 mg/mL

Box of 10 (NDC 0024-0595-01).

Store between 15° – 30° C (59° – 86° F).

CAUTION: Federal law prohibits dispensing without prescription.

REFERENCES

1. Osserman, K.E. and Kaplan L.I., *J.A.M.A., 150*: 265, 1952.
2. Osserman, K.E., Kaplan, L.I. and Besson, G., *J. Mt. Sinai Hosp., J.A.M.A., 20*:165, 1953.
3. Osserman, K.E.and Kaplan, L.I., *Arch. Neurol. & Psychiatr., 70*:385, 1953.
4. Osserman, K.E. and Teng, P., *J.A.M.A., 160*:153, 1956.
5. Osserman, K.E., and Genkins, G., *Ann. N.Y. Acad. Sci, 135*:312, 1966.
6. Tether, J.E., Second International Symposium Proceedings, Myasthenia Gravis, 1961, p. 444.
7. Tether, J.E., in H.F. Conn: *Current Therapy* 1960, Philadelphia, W.B. Saunders Co., p.551.
8. Tether, J.E., in HF Conn: *Current Therapy* 1965, Philadelphia, W.B. Saunders Co., p. 556.
9. Grob, D. and Johns, R.J., *J.A.M.A., 166*:1855, 1958

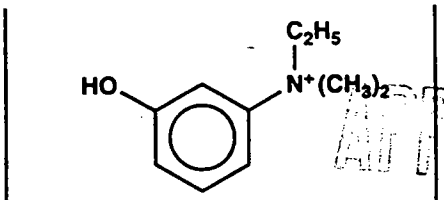
Printed in USA

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

Edrophonium Chloride Injection, USP

DESCRIPTION

Edrophonium chloride is a short and rapid-acting cholinergic drug. Chemically, edrophonium chloride is Ethyl (*m*-hydroxyphenyl) dimethylammonium chloride. The molecular formula is $C_{10}H_{16}ClNO$ and its structural formula is as follows:



M.W. 201.70

Edrophonium chloride is a white, odorless, crystalline powder. Its solution (1 in 10) is practically colorless. Very soluble in water; freely soluble in alcohol; insoluble in chloroform and in ether.

Each mL contains, in a sterile solution, 10 mg edrophonium chloride compounded with 0.45% phenol as a preservative, and 0.2% sodium metabisulfite as an antioxidant, buffered with sodium citrate and citric acid, and pH adjusted to approximately 5.4.

Edrophonium chloride injection is intended for IV and IM use.

CLINICAL PHARMACOLOGY

Edrophonium chloride is an anticholinesterase drug. Its pharmacological action is due primarily to the inhibition or inactivation of acetylcholinesterase at sites of cholinergic transmission. Its effect is manifest within 30 to 60 seconds after injection and lasts an average of 10 minutes.

INDICATIONS AND USAGE

Edrophonium chloride injection is recommended for the differential diagnosis of myasthenia gravis and as an adjunct in the evaluation of treatment requirements in this disease. It may also be used for evaluating emergency treatment in myasthenic crises. Because of its brief duration of action, it is not recommended for maintenance therapy in myasthenia gravis.

Edrophonium chloride is also useful whenever a curare antagonist is needed to reverse the neuromuscular block produced by curare, tubocurarine, gallamine triethiodide or dimethyl-tubocurarine. It is not effective against decamethonium bromide and succinylcholine chloride. It may be used adjunctively in the treatment of respiratory depression caused by curare overdosage.

CONTRAINDICATIONS

Edrophonium chloride injection is contraindicated in patients with a known hypersensitivity to anticholinesterase agents; intestinal and urinary obstructions of mechanical type.

WARNINGS

Whenever anticholinesterase drugs are used for testing, a syringe containing 1 mg of atropine sulfate should be immediately available to be given in aliquots intravenously to counteract severe cholinergic reactions which may occur in the hypersensitive individual, whether he is normal or myasthenic. Edrophonium chloride should be used with caution in patients with bronchial asthma or cardiac dysrhythmias. The transient bradycardia which sometimes occurs can be relieved by atropine sulfate. Isolated instances of cardiac and respiratory arrest following administration of edrophonium chloride have been reported. It is postulated that these are vagotonic effects.

Edrophonium chloride injection contains sodium metabisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

Usage in Pregnancy: The safety of edrophonium chloride during pregnancy or lactation in humans has not been established. Therefore, use of edrophonium chloride in women who may become pregnant requires weighing the drug's potential benefits against its possible hazards to mother and child.

15 mL
10 Multiple-Dose Vials

NDC 0074-2284-15
E-177

Edrophonium Chloride Injection, USP 10 mg/mL

Sterile – For IV or IM Use

15 mL
10 Multiple-Dose Vials

Edrophonium Chloride Injection, USP 10 mg/mL

(01) 1 030074 228415 5

15 mL
10 Multiple-Dose Vials

NDC 0074-2284-15
E-177

Edrophonium Chloride Injection, USP
10 mg/mL

Sterile – For IV or IM Use

Each mL contains 10 mg edrophonium chloride compounded with 0.45 % phenol as a preservative and 0.2 % sodium metabisulfite as an antioxidant, buffered with sodium citrate and citric acid, and pH adjusted to approximately 5.4.

Usual Dosage: See package insert.

Store between 15° – 30° C (59° – 86° F).

Caution: Federal law prohibits dispensing without prescription.

Rev. December 1997

Printed in USA

ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

15 mL
10 Multiple-Dose Vials

Edrophonium Chloride
Injection, USP
10 mg/mL

15 mL
Multiple-dose vial

NDC 0074-2284-15

Edrophonium Chloride Injection, USP 10 mg/mL

Sterile — For IV or IM Use

Store between 15° – 30° C (59° – 86° F).

Caution: Federal law prohibits dispensing without prescription

Rev. 12/97
Abbott Laboratories
N. Chicago, IL 60064, USA

Each mL contains 10 mg edrophonium chloride compounded with 0.45 % phenol as a preservative and 0.2 % sodium metabisulfite as an antioxidant, buffered with sodium citrate and citric acid and pH adjusted to approximately 5.4

(01) 0 30074 22841 5 8

EXP

LOT

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40131

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. 4

2. ANDA # 40-131

3. NAME AND ADDRESS OF APPLICANT
Abbott Laboratories, Inc.
Attention: Thomas F. Willer
D-389, Bldg. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-3537

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Edrophonium Chloride Inj. USP

9. AMENDMENTS AND OTHER DATES:

Firm		FDA	
Original sub.	12/30/94	Ack. letter	2/9/95
Amendment	06/06/96	N/A letter	5/12/95
Amendment	09/04/96		
Amendment	03/11/97	N/A letter	10/21/96
New Corres.	06/10/97	Fax Def.	06/19/97
Amendment	09/05/97		
Amendment	10/02/97		

10. PHARMACOLOGICAL CATEGORY
Cholinergic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Injection

14. POTENCY
10 mg/mL

15. CHEMICAL NAME AND STRUCTURE
N-Ethyl-3-hydroxy-N,N-dimethylbenzenaminium chloride
$C_{10}H_{16}ClNO$; M.W. 201.70

17. COMMENTS
See text of review.

18. CONCLUSIONS AND RECOMMENDATIONS
Application can be approved.

19. REVIEWER: Andrew J. Langowski

DATE COMPLETED: 09/25/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40131

BIOEQUIVALENCE REVIEW(S)

AUG 21 1995

Edrophonium Chloride Injection
10 mg/mL
ANDA #40-131
Reviewer: Moo Park
Filename: 40131W.D94

Sanofi Winthrop
New York, NY
Submission Date:
December 30, 1994

Review of a Waiver Request

I. Objective

Review of Sanofi Winthrop's waiver request for its Edrophonium Chloride Injection.

II. Comments

1. The formulations for the test product (Sanofi Winthrop) and the reference product, Tensilon^{R}, (ICN Pharmaceuticals) are considered identical except the antioxidant as shown in Table 1. Amount of buffers used for the reference product is not available in the COMIS. Sodium sulfite and sodium metabisulfite are antioxidants in the same chemical category.

Table 1. Formulation Comparison

Ingredient	Test Product, mg/mL	Reference product, mg/mL
Edrophonium Chloride, USP	10	10
Sodium Metabisulfite, NF		
Sodium Sulfite		
Sodium Citrate, Dihydrate, USP		
Citric Acid, Monohydrate, USP		
Phenol, USP		
Water for Injection, USP		

2. The drug product is an aqueous injectable solution. The

waiver is granted.

III. Recommendation

The Division of Bioequivalence agrees that the information submitted by Sanofi Winthrop demonstrate that Edrophonium Chloride Injection, 10 mg/mL strength, falls under 21 CFR Section 320.22 (b) of the Bioavailability/ Bioequivalence Regulations. The waiver of in vivo bioequivalence study for the 10 mg/mL strength of the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test injectable formulation, 10 mg/mL strength, to be bioequivalent to ICN Pharmaceuticals' Tensilon®, 10 mg/mL strength.

The firm should be informed of the recommendation.

Moo Park, Ph.D.
Chemist, Review Branch III
Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE
Ramakant M. Mhatre, Ph.D. 7/5/95
Branch Chief, Review Branch III
Division of Bioequivalence

Concur: Date: 8/21/95
Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

cc: ANDA #40-131 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-658 (Mhatre, Park), Drug File, Division File

COMPONENTS AND COMPOSITION

INGREDIENTS	PER ML
Edrophonium Chloride USP	10.0 mg
Sodium Metabisulfite NF (100% basis)	
Phenol USP	
Sodium Citrate USP	
Citric Acid USP	
Water for Injection USP	
Nitrogen NF	

The finished product specifications are as follows:

TEST	SPECIFICATION
Description	
Identification	
Assay (Edrophonium Chloride)	
Assay	
Assay	
Related Substances	Individual Total
Fill volume	
Sterility	
Bacterial Endotoxins	
pH	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40131

MICROBIOLOGY REVIEW(S)

Office for Generic Drugs, HFD-640
Microbiologist's Review
October 22, 1996

A. 1. **ANDA:** 40-131

APPLICANT: Sanofi Winthrop, Inc.
90 Park Avenue
New York, NY 10016

2. **PRODUCT NAME:** Edrophonium Chloride Injection, USP
3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** 10 mg/mL, 15 mL vials, intravenous or intramuscular injection
4. METHOD(S) OF STERILIZATION:
5. PHARMACOLOGICAL CATEGORY: Diagnostic Test for Myasthenia Gravis

B. 1. DATE OF INITIAL SUBMISSION: December 30, 1994
(Received Jan. 3, 1995)
2. DATE OF AMENDMENT: September 4, 1996
Subject of this Review (September 5, 1996)

3. RELATED DOCUMENTS: None
4. ASSIGNED FOR REVIEW: October 21, 1996

C. REMARKS: The amendment provides for the response to the microbiology deficiency letter, dated June 30, 1995.

D. CONCLUSIONS: This application is recommended for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes".

10/22/96

Andrea S. High, Ph.D.

cc:
Original **ANDA**
Duplicate ANDA
Division Copy
Field Copy
Drafted by A. High, HFD 640 x:wp\microrev\40-131a1
Initialed by F. Fang or F. Holcombe, Jr.

10/25/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40131

ADMINISTRATIVE DOCUMENTS

DIVISION REVIEW SUMMARY

ANDA: 40-131

FIRM: Abbott Laboratories, Inc.
D-389, Bldg. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-3537

Note: Previous application holder was Sanofi Pharmaceuticals.

DOSAGE FORM: Injection STRENGTH: 10 mg/mL

DRUG: Edrophonium Chloride USP

CGMP STATEMENT/EIR UPDATE STATUS: Acceptable 10/2/97.

BIO STUDY INFORMATION: In-vivo waiver submitted and granted 8/21/95.

METHODS VALIDATION: N/A; Drug substance and drug product are articles of the USP.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION? yes

The containers used in the stability study are of the same size and material as those described in the container section. The firm submitted accelerated stability data for the product packaged in both container sizes.

The firm requests an expiration date of 24 months based on the data submitted.

The stability tests and specifications are indicated in the following table:

The stability tests and specifications are as follows:

TEST	SPECIFICATION
Description	
pH	
Assay (Edrophonium Chloride)	
Assay (Sodium Metabisulfite)	

Assay	
Degradation Products	
Sterility*	
Bacterial Endotoxins**	
APHA Color	

*Testing performed initially, annually and at exp. date.
**Testing performed initially and at exp. date.

LABELING: Acceptable. See review dated 4/1/97 and 1/14/98.

STERILIZATION VALIDATION: Acceptable. See review dated 10/22/96.

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?)

No information on bio-batch since a waiver was granted.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)

Stability batch (lot #PD4-365) of adequate size. Process the same. Firm requests 24 months expiration dating.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

The intended production batch size is 550 liters.

RECOMMENDATION: Approvable.

SIGNATURE: A. Jangouski DATE: 1/15/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 40131

CORRESPONDENCE

ABBOTT

ORIG AMENDMENT
N/AM

Hospital Products Division
Abbott Laboratories
[illegible], Bldg. AP30
[illegible] Abbott Park Road
Abbott Park, Illinois 60064-3537

October 2, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD #630
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

ATTENTION: Douglas Sporn
Director

VIA FAX 301-443-3839 and Paper Copy

Re: ANDA 40-131 Edrophonium Chloride Injection, USP

Abbott Laboratories hereby responds to a telephone request on October 2, 1997 from Mr. Andrew Langowski, OGD, to Dr. Thomas Willer, Abbott Laboratories. The Agency observed that the pending ANDA did not include a finished product specification for degradation products / related compounds in compliance with current OGD policy. Upon review, we have added the requested addition of degradation products / related compounds testing to the finished product test requirements. We also added the specification limits. Please see Attachment 1. We also revised the [illegible] include this testing. Please see Attachment 2.

We trust that this ANDA amendment is complete. If you have any questions or need clarification, please telephone me at your earliest convenience.

Sincerely,

ABBOTT LABORATORIES

Thomas F. Willer

RECEIVED
OCT 0 6 1997
GENERIC DRUGS

Thomas F. Willer, Ph.D.
Assistant Director, Regulatory Affairs
Hospital Products Division
Phone: (847) 937-6845
Fax: (847) 938-7867
Internet: WILLETF@hpd.abbott.com

TFW:tw

g:10-97f.tfw/15
Attachments

noted
DS 9/11/97

ABBOTT

Hospital Products Division
Abbott Laboratories
D-389, Bldg. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-3537

AMENDMENT

September 5, 1997

RECEIVED

SEP 08 1997

GENERIC DRUGS

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD # 630
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ATTENTION: Douglas Sporn
Director

Re: ANDA 40-131 Edrophonium Chloride Injection USP, 10 mg/mL
MINOR AMENDMENT

Abbott Laboratories hereby amends the above-referenced abbreviated new drug application for the subject drug. Reference is made to our abbreviated new drug application dated December 18, 1996, submitted pursuant to § 505(j) of the Federal Food, Drug, and Cosmetic Act, for Edrophonium Chloride Injection USP, 10 mg/mL. Reference is also made to Dr. Frank Holcombe's facsimile dated June 19, 1997, regarding our correspondence dated September 4, 1996 and March 11, 1997. For your convenience, we have included a copy of the June 19, 1997 correspondence immediately following this letter.

COMMENT: **"Please note that it is stated in the General Notices of USP 23 under Added Substances that "Unless otherwise specified... suitable substances such as antimicrobial agents... are regarded as unsuitable and are prohibited unless...they do not interfere with the assays and tests prescribed for determining compliance with the Pharmacopeial standards.**

While Phenol is an excipient found in your product as well as the innovator product, the anti-oxidant sodium metabisulfite is not. Please note that the currently marketed edrophonium chloride injection products, previously approved by the FDA, pass testing by the USP assay method as shown by method verification conducted by FDA laboratories.

We request that you provide additional data to support your contention that the USP method is not suitable. Please analyze, using the USP assay method, samples of currently marketed product manufactured by at least two different manufacturers (including the innovator) and submit the results for review.

In addition, you should evaluate the use of sodium metabisulfite in place of sodium sulfite as an antioxidant as a potential causative factor for the inability to precisely quantitate edrophonium chloride. Please note that the excipient also

Sept 10 1997

RESPONSE: We note and acknowledge that it is stated in the General Notices of USP 23 under Added Substances that "Unless otherwise specified...suitable substances such as antimicrobial agents...are regarded as unsuitable and are prohibited unless...they do not interfere with the assays and tests prescribed for determining compliance with the Pharmacopeial standards.

While phenol is an excipient found in our product as well as the innovator's product, we also note and acknowledge that our formulation contains an anti-oxidant sodium metabisulfite rather than sodium sulfite as found in the innovator's product. We have submitted a request for waiver from the in vivo bioavailability requirements on Page 46 of the original submission. For your convenience, a copy of the waiver is included in Exhibit I. Furthermore, we note and acknowledge that the currently marketed edrophonium chloride injection products, previously approved by the FDA, pass testing by the USP assay method as shown by method verification conducted by FDA laboratories.

Exhibit II contains additional data, including
obtained from samples of currently marketed product manufactured by three different manufacturers (including the innovator) using both the USP assay method by

In addition, since we have shown in our March 11, 1997 correspondence that the

when analyzed using the USP assay method and based upon the Agency recommendation, we have evaluated the use of sodium metabisulfite versus sodium sulfite as a causative factor for the inability to precisely quantitate edrophonium chloride. Exhibit III contains copies for placebo and sodium sulfite showing interference. Although the does not exist in formulation with sodium sulfite, the variability in the efficiency still has an impact on the accuracy of the assay. Please refer to Exhibit II.

Abbott Laboratories hereby certify that we have sent a true copy of this submission to Mr. W. Michael Rogers of the Lenexa, Kansas FDA District Office. This document consists of Confidential and/or Trade Secret information subject to 18 U.S. C. 1905 and to which all claims of Privilege and Confidentiality are asserted in both statutory and common law.

Sincerely,

ABBOTT LABORATORIES

Thomas F. Willer

Thomas F. Willer, Ph.D.
Assistant Director, Regulatory Affairs
Hospital Products Division
Phone: (847) 937-6845
9-97f.tfw/5 - Attachment

JUN 19 1997

38. Chemistry Comments to be Provided to the Applicant

ANDA: 40-131 APPLICANT: Sanofi Winthrop, Inc.

DRUG PRODUCT: Edrophonium Chloride Injection USP, 10 mg/mL

The deficiencies presented below represent FACSIMILE deficiencies.

Deficiencies:

Please note that it is stated in the General Notices of USP 23 under Added Substances that "Unless otherwise specified ... suitable substances such as antimicrobial agents ... are regarded as unsuitable and are prohibited unless ... they do not interfere with the assays and tests prescribed for determining compliance with the Pharmacopeial standards.

While phenol is an excipient found in your product as well as the innovator product, the anti-oxidant sodium metabisulfite is not. Please note that the currently marketed edrophonium chloride injection products, previously approved by the FDA, pass testing by the USP assay method as shown by method verification conducted by FDA laboratories.

We request that you provide additional data to support your contention that the USP method is not suitable. Please analyze, using the USP assay method, samples of currently marketed product manufactured by at least two different manufacturers (including the innovator) and submit the results for review.

In addition, you should evaluate the use of sodium metabisulfite in place of sodium sulfite as an antioxidant as a potential causative factor for the inability to precisely quantitate edrophonium chloride. Please note that this excipient also

Sincerely yours,

/s/

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

FACSIMILE AMENDMENT

JUN 19 1997

ANDA/~~AADA~~: 40-131

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 [redacted]

TO: APPLICANT Sanofi Winthrop Inc. PHONE (212) 551-4230
ATTN: Gregory Torre, Ph.D., J.D. FAX (212) 551 4912
or John Purpura

FROM: Kassandra Sherrod, PROJECT MANAGER (301-594-1300)

Dear Sir~~Madam~~:

This facsimile is in reference to your abbreviated new drug/~~antibiotic~~ application dated December 30, 1996, submitted pursuant to Section 505(j)/~~507~~ of the Federal Food, Drug, and Cosmetic Act for Edrophonium Chloride Injection USP, 10 mg/mL

Reference is also made to your amendment(s) dated September 4, 1996 and March 11, 1997.

Attached are 1 pages of minor deficiencies and/or comments that should be responded to within 30 calendar days from the date of this document. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your complete response should be (1) faxed directly to our document control room at 301- 827-4337, (2) mailed directly to the above address, and (3) the cover sheet should be clearly marked a FACSIMILE AMENDMENT.

Please note that if you are unable to provide a complete response within 30 calendar days, the file on this application will be closed as a MINOR AMENDMENT and you will be required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Accordingly, a response of greater than 30 days should be clearly marked MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Facsimiles or incomplete responses received after 30 calendar days will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. You have been/~~will be~~ notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data.

SPECIAL INSTRUCTIONS:

X:\new\ogdadmin\faxtrak\faxcov.fax

SANOFI WINTHROP, INC.
90 PARK AVENUE
NEW YORK, NY 10016-1389
TELEPHONE 212 551 4000

sanofi WINTHROP

March 11, 1997

VIA FEDERAL EXPRESS

Mr. Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NDA ORIG AMENDMENT
N/Arm

MINOR AMENDMENT

Re: ANDA 40-131; Edrophonium Chloride Injection USP, 10 mg/mL

Dear Mr. Sporn:

Reference is made to our abbreviated new drug application dated December 30, 1994, submitted in pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Edrophonium Chloride Injection USP, 10 mg/mL.

Reference is also made to Dr. Frank Holcombe's correspondence dated October 21, 1996 regarding our amendment dated June 6, 1996. Contained herein, please find our response to Dr. Holcombe's letter in **comment**/response format. For your convenience, we have included a copy of the October 21, 1996 correspondence immediately following this letter.

A. Chemistry Deficiencies

GENERIC DRUGS

In addition, we advise you to contact the FDA District laboratory in Kansas in order to resolve or clarify any matters regarding the performance of the methods.

Updated 24 months controlled room temperature stability data for the exhibit batch (PD4-365, Split A & Split B) is contained in Attachment 2.

B. Labeling Deficiencies

All of the labeling comments have been addressed. Changes are reflected in the twelve copies (6 archival and 6 review copy) of final printed container labels and carton and package insert labeling. We have also included a side-by-side comparison with our previous submission to be in accord with 21 CFR 314.94(a)(8)(iv).

Sanofi Winthrop, Inc. hereby certifies that we have sent a true copy of this cover letter to Mr. Edward T. Warner, District Director of the New York FDA District Office, and a true copy of this submission to Mr. W. Michael Rogers of the Lenexa, Kansas, FDA District Office, as per Mr. Warner's instructions.

This document consists of Confidential and/or Trade Secret information subject to 18 U.S.C. 1905 and to which all claims of Privilege and Confidentiality are asserted in both statutory

and common law.

If you require any clarification or further information, please call Mr. John Purpura, Manager CMC at (212) 551-4261.

Sincerely,

John Purpura /for

Gregory M. Torre, Ph.D., J.D.
Senior Director
Drug Regulatory Affairs

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

ANDA 40-131

Sanofi Winthrop, Inc.
Attention: Gregory M. Torre, Ph.D., J.D.
90 Park Avenue
New York, NY 10016

OCT 21 1996

Dear Madam:

This is in reference to your abbreviated new drug application dated December 30, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Edrophonium Chloride Injection USP, 10 mg/mL.

Reference is also made to your amendment dated June 6, 1996.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

B. Labeling Deficiencies

1. CONTAINER - 15 mL

Revise the storage recommendation statement to read as it was previously requested, "Store between 15°-30°C (59°-86°F)".

2. CARTON - 10s x 15 mL

a. See comment under CONTAINER.

b. Revise the "Usual Dosage" statement to read:

Usual Dosage: See package insert.

3. INSERT

a. DESCRIPTION

i. Revise the chemical name to read:

Ethyl (*m*-hydroxyphenyl) ... [capital "E" and italic "*m*", per USP 23.]

ii. Per the USP 23 Description and Solubility Reference Table, insert the following text as the second paragraph:

Edrophonium chloride is a white, odorless, crystalline powder. Its solution (1 in 10) is practically colorless. Very soluble in water; freely soluble in alcohol; insoluble in chloroform and in ether.

b. DOSAGE AND ADMINISTRATION

i. Intravenous Dosage (Adults), line 4

... needle is left *in situ*. *Only* if no reaction ... [Note italic print.]

ii. Edrophonium Chloride Injection Test in Crisis

A). Paragraph 1, line 1 - Italicize the word "crisis".

B). Paragraph 2, sentence 3 - Italicize "Dosage used at this time is most important:"

c. HOW SUPPLIED

See comment under CONTAINER.

d. REFERENCES

We note a combination of omission, editorial, and spelling errors in this section. Revise this section to be in accord with the REFERENCES section as it appears in the approved insert labeling of the listed drug, Tensilon® (Hoffmann LaRoche, Inc.; Permitted 12-29-87; Issued 2/87). Please carefully proofread prior to submission.

Please revise your container labels, and carton and insert labeling, as instructed above, and submit 12 copies of final printed labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison with your last submission with all differences annotated and explained.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MINOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

[redacted] INC.

sanofi

NEW CORRESP
NC

10, 1997

NDA 40-131

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

. Douglas Sporn
rector
fice of Generic Drugs
nter for Drug Evaluation and Research
od and Drug Administration
ocument Control Room
etro Park North II
00 Standish Place, Room 150
ockville, Maryland 20855-2773

bject: Edrophonium Chloride Injection USP, 10 mg/mL
ANDA 40-131

ear Mr. Sporn:

accordance with 21CFR 314.72(a)(1), effective June 10, 1997, Sanofi Pharmaceuticals, Inc. is transferring ownership of the nufacturing facility at 1776 North Centennial Drive, McPherson, KS 67460 and the subject ANDA to a new owner:

Abbott Laboratories
100 Abbott Park Road
Abbott Park, IL 60064-3500

ease use the above address for future correspondence.

is document consists of Confidential and/or Trade Secret Information subject to 18 U.S.C. 1905 and to which all claims of vilege and Confidentiality are asserted in both statutory and common law.

you have any questions, please contact Irina Privin at (212) 551-4221.

RECEIVED
JUN 16 1997
GENERIC DRUGS

Sincerely yours,

Gregory M. Torre, Ph.D., J.D.
Senior Director
Drug Regulatory Affairs

Dave Guzek, Abbott Laboratories
Sandra Harder, Abbott Laboratories

ANDA 40-131

Sanofi Winthrop, Inc.
Attention: Linda L. Nardone, Ph.D.
90 Park Avenue
New York, NY 10016

MAY 12 1995

Dear Madam:

This is in reference to your abbreviated new drug application dated December 30, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Edrophonium Chloride Injection USP, 10 mg/mL.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

3. **Regarding product stability:**

B. Labeling Deficiencies

CONTAINER: 15 mL - Multiple dose vial

1. Please indicate that the vial is a multiple dose vial.

2. Revise the temperature storage recommendations to read:

   Store between 15° to 30°C (59° to 86°F).

3. "cll" should read "call" at the bottom of the label.

CARTON: 10 x 15 mL

1. See comments 2 and 3 under CONTAINER.

2. Revise to read: "USUAL DOSAGE: See package insert..."

INSERT:

1. DESCRIPTION

   Please include the molecular weight and molecular formula.

2. ACTIONS

   Revise this section heading to read:

   CLINICAL PHARMACOLOGY

3. INDICATIONS

   a. Revise this section heading to read:

      INDICATIONS AND USAGE

   b. Paragraph 1, line 1 - Revise to read:

      Edrophonium chloride injection is recommended...

4. CONTRAINDICATIONS

   Edrophonium chloride injection is contraindicated in patients with a known...

5. WARNINGS

Paragraph 2, second and third sentences - Revise to read:

"Sulfite sensitivity..." rather than "metabisulfite"...

6. DOSAGE AND ADMINISTRATION

a. Edrophonium Chloride Test for Evaluation of Treatment Requirements in Myasthenia Gravis - Table.

Realign the table so that the columns appear directly below the column headings in which they are intended.

b. Adequate Response, line 1 - Replace the colon with a semi-colon.

7. OVERDOSAGE

a. Insert the following text to appear as #4:

Pralidoxime chloride (a cholinesterase reactivator) may be given intravenously at the rate of 50 to 100 mg per minute; usually the total dose does not exceed 1000 mg. Extreme caution should be exercised in the use of pralidoxime chloride when the cholinergic symptoms are induced by double-bond phosphorous anticholinesterase drugs.[9]

b. Your current #4 should be revised to read #5.

c. This section should be relocated to appear before the DOSAGE AND ADMINISTRATION sections.

8. HOW SUPPLIED

Revise the "CAUTION: Federal Law" statement to read:

...prohibits dispensing without prescription.

9. REFERENCES

a. Insert a comma after the authors last name in all references listed. [e.g., Osserman, K.E.]

b. If there are more than one author listed, insert "and" before the last author's name. [e.g., Osserman, KE and Kaplan, L.I.]

c. Insert the following to appear as reference #9:

Grob, D. and Johns, R.J., *J.A.M.A.*, *166*:1855, 1958.

Please revise your container labels, carton and insert labeling, then prepare and submit final printed container labels and carton labeling and draft insert labeling.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. You will be notified in a separate letter of any deficiencies identified in the bioequivalence portion of your application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

5/10/95

Frank O. Holcombe, Jr., Ph.D.
Acting Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

SANOFI WINTHROP INC
90 PARK AVENUE
NEW YORK, NY 10016-1389
TELEPHONE 212 551 4000

Sanofi WINTHROP

September 4, 1996

NDA ORIG AMENDMENT
N/AS

VIA FEDERAL EXPRESS

RECEIVED

SEP 0 5 1996

GENERIC DRUGS
MICRO/STERILITY
ASSURANCE
CORRESPONDENCE

Mr. Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Re: ANDA 40-131; Edrophonium Chloride Injection USP, 10 mg/mL

Dear Mr. Sporn:

Reference is made to our abbreviated new drug application dated December 30, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Edrophonium Chloride Injection USP, 10 mg/mL.

Reference is also made to Ms. Florence Fang's correspondence dated June 30, 1995 regarding the sterilization data submitted December 30, 1994. Contained herein, please find our response to Ms. Fang's letter in **comment**/response format. For your convenience, we have included a copy of the June 30, 1995 correspondence immediately following this letter.

PAGES 1-8 REMOVED
CONTAIN TRADE SECRET INFORMATION

The above standards are based on the manufacturer's recommendation for the instrument.

Sanofi Winthrop, Inc. hereby certifies that we have sent a true copy of this cover letter to Mr. Edward T. Warner, District Director of the New York FDA District Office, and a true copy of this submission to Mr. W. Michael Rogers of the Kansas City, Kansas, FDA District Office, as per Mr. Warner's instructions.

This document consists of Confidential and/or Trade Secret information subject to 18 U.S.C. 1905 and to which all claims of Privilege and Confidentiality are asserted in both statutory and common law.

If you require any clarification or further information, please call Mr. John Purpura, Manager CMC, at (212) 551-4261.

Sincerely,

John Purpura /for

Gregory M. Torre, Ph.D., J.D.
Senior Director
Drug Regulatory Affairs

SANOFI WINTHROP, INC.
90 PARK AVENUE
NEW YORK, NY 10016-1389
TELEPHONE 212 907 3500

sanofi WINTHROP

DEC 30 1994

MICRO/STERILITY ASSURANCE INFORMATION ENCLOSED

Labeling reviewed completed 3/6/95

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Dear Sir/Madam:

Submitted herewith in duplicate, under 21 CFR 314.50 is an original Abbreviated New Drug Application for Edrophonium Chloride Injection USP, 10 mg/mL, vial.

Edrophonium Chloride Injection is listed in "Approved Drug Products with Therapeutic Equivalence Evaluations," 14th Edition, page 3-106. A copy appears in Section II.

The active ingredient, indications, concentration, route of administration, and conditions of use for Edrophonium Chloride Injection, are the same as those of the innovator's product, Tensilon®, manufactured by Roche for ICN Pharmaceuticals, Inc. Comparative information is attached in Section IV.

The labeling is the same in content as that of the innovator's drug Tensilon®, except for the antioxidant and changes that are necessary due to a change in manufacturer and editorial changes. A copy of the innovator's package insert is provided in Section V for your convenience.

Development work on Sanofi Winthrop's injectable drug product was performed using Enlon®, the market leader. Enlon® has the same formulation as Tensilon®, the innovator. A copy of Enlon's® insert is also provided in Section V.

The first three production batches of Edrophonium Chloride Injection USP, 10 mg/mL, vial, will be placed into our stability program and reported at regular intervals for as long as necessary to support the proposed 24-month expiration date. Furthermore, we agree to withdraw from the market any batch found to fall outside the specifications for this product.

The Sponsor of this Abbreviated New Drug Application is Sanofi Winthrop, Inc. The product is manufactured at the McPherson, Kansas, facility, which is registered under the name Sanofi Winthrop, Inc. However, the product, when approved, will be marketed by Kanetta Pharmacal which is an affiliate of Sanofi Winthrop, Inc. The labeling included in this application reflects the name Kanetta Pharmacal. There may be internal documents and correspondence to/from vendors and contract facilities that reflect the old name Sterling Winthrop Inc. and the name Sanofi Winthrop Pharmaceuticals which is an affiliate of Sanofi Winthrop, Inc. Please be aware of this when reviewing the application.

We hereby certify that we have sent a true copy of this cover letter to Mr. Edward T. Warner, District Director of the New York FDA district office, and a true copy of this original submission to the Kansas City, KS FDA district office, as per Mr. Warner's instructions.

Any inquiries concerning this Abbreviated New Drug Application should be addressed to:

Linda L. Nardone, Ph.D.
Vice President
Drug Regulatory Affairs
Sanofi Winthrop, Inc.
90 Park Avenue
New York, NY 10016

Your attention to this application is greatly appreciated.

Sincerely,

Shirley Ternejik

for Linda L. Nardone, Ph.D.
Vice President
Drug Regulatory Affairs

LLN/ST:ls

SANOFI WINTHROP, INC.
90 PARK AVENUE
NEW YORK, NY 10016-1389
TELEPHONE 212 551 4000

ORIGINAL

sanofi WINTHROP

RECEIVED

Labeling Review Completed 5.26.96 Discipline

JUN 10 1996

GENERIC DRUGS

June 6, 1996

VIA FEDERAL EXPRESS

Mr. Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NDA ORIG AMENDMENT

MAJOR AMENDMENT

Subject: ANDA 40-131; Edrophonium Chloride Injection USP, 10 mg/mL

Dear Mr. Sporn:

Reference is made to our abbreviated new drug application dated December 30, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Edrophonium Chloride Injection USP, 10 mg/mL.

Reference is also made to Dr. Frank Holcombe's correspondence dated May 12, 1995. Contained herein, please find our response to Dr. Holcombe's letter in **comment**/response format. For your convenience, we have included a copy of the May 12, 1995 correspondence immediately following this letter.

A. Chemistry Deficiencies

THROUGH PAGE 5 REMOVED AS TRADE SECRET INFORMATION

B. Labeling Deficiencies

All of the labeling comments have been addressed. Changes are reflected in the twelve copies of final printed container labels and container labeling and four copies of draft insert labeling contained in Attachment 8.

Sanofi Winthrop, Inc. hereby certifies that we have sent a true copy of this cover letter to Mr. Edward T. Warner, District Director of the New York FDA District Office, and a true copy of this submission to Mr. W. Michael Rogers of the Lenexa, Kansas, FDA District Office, as per Mr. Warner's instructions.

This document consists of Confidential and/or Trade Secret information subject to 18 U.S.C. 1905 and to which all claims of Privilege and Confidentiality are asserted in both statutory and common law.

If you require any clarification or further information, please call Mr. John Purpura, Manager CMC, at (212) 551-4261.

Sincerely,

John Purpura / for

Gregory M. Torre, Ph.D., J.D.
Senior Director
Drug Regulatory Affairs

ANDA 40-131

Sanofi Winthrop, Inc.
Attention: Linda L. Nardone, Ph.D.
90 Park Avenue
New York, NY 10016

FEB 9 1995

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Edrophonium Chloride Injection USP, 10 mg/mL, 15 mL vials

DATE OF APPLICATION: December 30, 1994

DATE OF RECEIPT: January 3, 1995

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Kassandra Sherrod
Consumer Safety Officer
(301) 594-1300

Sincerely yours,

2/9/95

Yana Ruth Mille
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research